

**Management Of Early Carious Lesions And Reduction Of Caries Incidence In Caries-Active  
Or At-Risk Individuals -  
- Antimicrobial Agents**

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*Abstract:*

Dental caries is an infectious disease of bacterial origin. The use of antimicrobial agents to reduce or eliminate the bacteria associated with caries follows the approach used to combat other infectious diseases of humans. Unfortunately, only a few dozen studies have sufficient resolving power to make inferences as to the anticaries efficacy of the antimicrobial approach to caries management. Here, we comment on the findings of the RTI/UNC review concerning antimicrobials, discuss additional findings not covered in that review, and make recommendations based upon both the available literature and from our own experience. Even though the studies published thus far are inconclusive or lack sufficient demonstration of efficacy to recommend a specific approach involving antimicrobial agents in routine clinical practice, several pieces of information from these studies suggest future avenues of investigation.

*Keywords:* antimicrobial agents, chlorhexidine, fluoride, surrogate markers, clinical trials, mutans streptococci, chemotherapeutic approach

Because dental caries is an infectious disease of bacterial origin, antimicrobial agents constitute a reasonable approach toward attenuating not only the bacterial biofilm *in situ*, but also its transmission from host to host. These approaches, while limited based upon certain constraints inherent to the oral cavity, have their roots in early attempts at plaque control and extend from mechanical approaches to chemical approaches. Although this extension to present-day chemotherapeutic approaches seems well reasoned and grounded in the best traditions of the “medical model”, several assumptions that underpin the chemotherapeutic approach need re-examination. For example, a global reduction of the plaque biofilm mass may not lead to the desired effect of selectively eliminating or reducing the caries-associated microorganism. The exception to this may be fluoride for differential suppression of mutans streptococci, which has been shown in artificial plaque models.<sup>1</sup> Thus, the aim of antimicrobial approach for the control of caries should be aimed not toward elimination of all the plaque microorganisms but toward effecting an ecological shift from a cariogenic to a non-cariogenic biofilm.

The 22 studies (29 interventions) reviewed by the RTI/UNC were evaluated based on the effects of antimicrobials in reducing or preventing dental caries.<sup>2</sup> With the exception of a single study,<sup>3</sup> which was not included in the RTI/UNC review because it was only recently published, none met all the inclusion criteria for a well executed, double-blind, controlled clinical trial. Rather, these studies were proof of concept studies, with mutans streptococci levels as surrogate outcomes. While all 29 interventions were able to show reductions in MS levels, their effect on caries was marginal (0 to 40%). In this review, we will summarize the various trials using antimicrobials, comprised mainly of various formulations of chlorhexidine, along with other less studied antimicrobials. In addition, we will select a few studies we feel point to important areas worthy of future studies.

## **SPECIFIC COMMENTS ON THE RTI/UNC REPORT**

RTI/UNC evidence report addresses the efficacy of the non-surgical methods available for stopping or reversing the progression of a non-cavitated caries lesion in a primary or a permanent tooth, and the efficacy of the methods available for reducing the incidence of new coronal caries in primary and permanent teeth among individuals who are deemed to be ‘caries-active’ or at ‘high-risk’.<sup>2</sup> This systematic search was based on a detailed search of the relevant English language literature for human studies reported between 1966 – October 19999 using MEDLINE, EMBASE, and the Cochran Controlled Trial Register. The search did not include gray literature. The search was based on key words for methods such as fluoride, pit and fissure sealants, health education, dental prophylaxis, oral hygiene, dental plaque, chlorhexidine, dental sealants, cariostatic agents, and study characteristics and designs. The search was restricted to *in-vivo* studies that utilized methods applied or prescribed in a professional setting and that included a comparison group. For the search related to non-cavitated lesions, the search was restricted to studies where the unit of analyses was the individual lesion. For the search on high-risk individuals, a broader definition of individual risk based on caries experience and/or mutans streptococci levels was utilized.

The quality of each report was assessed using a 20 point scale based on study design, sample size, duration, blinding, confounders, baseline comparability, loss to follow-up, analysis, reliability, and internal and external validity. The raw quality scores were rescaled to a 0-100 scale. A four-level grading scheme was then used to grade the overall evidence in relation to the clinical question being asked. The grading system was based on the number of studies, the magnitude of the effect, the

quality rating score for the report, and the consistency of evidence across reports. This grading system rated evidence as either ‘good’, ‘fair’ (inconsistent), ‘poor’ (no more efficacious than placebo), or ‘incomplete’ (limited number of studies and/or poor methods).

### **A review of the RTI/UNC report**

The systematic review on the management of the non-cavitated lesion yielded 5 studies that included 2,292 lesions, 2 of which were randomized clinical trials. The therapeutic agents ranged from APF solution, 8 percent stannous fluoride, ammonical silver nitrate, 0.5 percent NaF rinse, 2 percent NaF solution, 5 percent NaF varnish, 0.2 percent NaF rinse, and sealants. Frequency of application of the agent ranged from one application at baseline to twice per month, once a week for three weeks with the pattern repeating at three months, every two to three months, and sealants repaired as needed. None of the studies were related to primary teeth.

The RTI/UNC report gave this heterogeneous group of studies quality scores between 40-65. The dental sealant study showed that lesion progression was at least five times higher in the comparison group. Two studies had data on lesion progression, which was similar in both experimental and control groups. The RTI/UNC report concluded that there is ‘incomplete’ evidence for the efficacy of professionally applied fluoride treatment for stopping and reversing non-cavitated lesions. It also concluded that the evidence is ‘incomplete’ for the efficacy of methods other than fluoride therapies for stopping or reversing the progression of non-cavitated lesions.

### **The management of caries active individuals**

The RTI/UNC report related to the above question is based on 22 studies that included 4363 subjects and 29 interventions. These studies were also heterogeneous in terms of study methods and subject characteristics. The 29 interventions included nine fluoride studies, eight chlorhexidine, six combinations, and six other interventions. Comparison groups were placebo, nil group, or active treatment group. Caries examination was based on visual/tactile and radiographs (17 studies), visual/tactile alone (5 studies), visual/tactile, radiographs, and FOTI (3 studies), visual only (2 studies), and visual/tactile for anterior teeth and radiographs for posterior teeth (1 study). These studies obtained quality scores between 25-80. Based on their systematic review, RTI/UNC report concluded that the evidence for the efficacy of topical fluoride application and fluoride rinses in the prevention of caries in caries-active and ‘at-risk’ individuals is ‘incomplete’. Similarly, the evidence for chlorhexidine gels, varnishes, and rinses, or the combination therapy was rated as ‘suggestive but incomplete’.

Even though the above systematic review seems thorough, a few issues need to be addressed to make recommendations concerning the best method of managing caries and future research. These include the studies reported after 1999 and the studies that looked at intermediate end-points such as mutans streptococci levels as a surrogate outcome for caries and subsequent development of caries among these individuals. We would like to mention five additional studies in this regard.

Using 1240 11-13 year old Scottish school children who were deemed to be at high risk on the basis of past caries experience and high mutans streptococci levels, Forgie et al. demonstrated

that four to six applications of 10 percent chlorhexidine varnish within a year reduced the levels of mutans streptococci levels, but failed to reduce caries increment over a period of three years.<sup>3</sup> They suggest that the inadequate frequency of varnish application may have been one reason for the failure to reduce caries incidence. This study is a well designed, adequately powered, and well carried out randomized clinical trial with four arms. The evaluation of the caries status was based on well-defined criteria that combined clinical, FOTI, and radiographic examinations. If we use the RTI/UNC quality score, this study would yield a quality score of 80. However, the addition of this study would not change the overall grading of the evidence.

Kohler et al. have demonstrated that reducing the levels of MS in stimulated saliva below  $3 \times 10^5$  CFU per mL in mothers with initially high mutans streptococci levels ( $>10^6$ ) resulted in significantly fewer infants becoming colonized with MS compared with a control group.<sup>4</sup> When the infants reached three years of age, 19 percent of the treatment group was infected with mutans streptococci compared with 63 percent in the control group. The long-term follow-up of this cohort indicated that 77 percent of treatment group children had caries by age seven compared to 91 percent in the control group, which was statistically significant.<sup>5</sup> The reason why this study was not included in the RTI/UNC report is perhaps because the intervention strategy was a combination that involved self-care and professional care.

Using a similar approach, Dasanayake et al. reported that application of NaF/Iodine varnish (6 applications) to the teeth of mothers with high levels of mutans streptococci around the time the infants are getting their primary teeth did not significantly reduce the colonization of mutans streptococci or the subsequent caries experience.<sup>6</sup> While the number of subjects who experienced

caries by the last study visit was too small in this study to draw meaningful inferences, this study also addresses the infrequent application of agents, and the incorrect timing of the application as possible reasons for the lack of positive results. Overall, there is a need for further studies to refine the intervention protocols in terms of frequency of application of agents, the timing of application, and sufficient follow-up among other issues.

The last report that is worth mentioning in relation to the caries inhibiting effect of chlorhexidine treatment is the meta-analysis reported by Rijkom et al.<sup>7</sup> Based on eight reports published between 1975-1994, Rijkom et al. reported that the over all caries inhibiting effect of the chlorhexidine treatment studies was 46 percent [95% CI of 35%-57%]. While some of the studies included in the above analysis also were included in the RTI report, this quantitative analysis of data as opposed to the systematic review perhaps tip the grading of evidence from ‘suggestive but incomplete’ to ‘strongly suggestive but incomplete.’

### **Additional studies - Kanamycin**

Based upon the specific plaque hypothesis,<sup>8</sup> Loesche and coworkers conducted a randomly designed clinical trial in 1977.<sup>9</sup> They found that kanamycin gel treatment before and after the placement of dental restorations significantly reduced the fissure levels of *S. mutans* by five-fold compared to a placebo gel treatment, but there was no alteration in the pooled approximal plaque samples. Interestingly, after the restorative treatment, salivary *S. mutans* levels were significantly decreased for both experimental and placebo groups. The treatment alone, in the absence of open caries lesions, might have influence the level of *S. mutans* in saliva. In retrospect, a control

group without gel applications should have been included in the study. That would help to eliminate the confounding effect due to the restorative treatment.

The study suggested that the kanamycin treatment was effective in reducing the bacterial count in the fissure. It was also reported that kanamycin could cause a nonspecific reduction of total plaque bacterial levels, and a significant increase in the proportions of *S. mutans* versus *S. sanguinis* in the plaque flora. This shift was not considered undesirable by the investigators.

Although the study found kanamycin gel treatment was associated with an overall 46 percent reduction of new carious surfaces in the 14-37 month period following the gel treatment, at the nine-month recall visit, the kanamycin treated subjects had seven times more new decayed surfaces than the placebo subjects. The investigators explained the accelerated rate of caries development by kanamycin treatment causing the focal proliferation of *S. mutans* buried in the pre-clinical carious lesions after eliminating all bacteria on the tooth surfaces. An antimicrobial agent that is capable of penetrating into the subsurface lesion, perhaps sodium fluoride, might be the agent of choice.

### **Topical applications of Vancomycin**

Vancomycin, an antibiotic effective against most gram-positive cocci and spirochetes, was tested as a possible plaque control agent *in vitro* and *in vivo*.<sup>10-12</sup> In a randomised clinical trial, 25 9 to 15 year old school children were treated with either 15 percent vancomycin gel (vancomycin hydrochloride) or as controls, and 24 dental hygiene students were treated with one percent vancomycin paste or as controls. They all were treated twice a day for five consecutive school

days.<sup>12</sup> The study reported a decrease in total cultivable bacterial levels and a temporary suppression of the prevalence of *S. mutans* after the treatment in the experimental group compared with the control groups.

There was another clinical study of the supervised application of vancomycin gel for two hundred 9 to 11 year old school children followed-up for 12 months.<sup>11</sup> The study found a significant difference in caries increment in treated subjects compared with the controls. However, this difference occurred only on fissure surfaces, and not on the smooth or the approximal surfaces.

The conclusions of these studies need to be reviewed with caution. One issue is that there was no clear detailed dental exam records of all the subjects participated in these studies. One study did not display the comparison of the DMF and OHI scores between the experimental and control groups. In the other study, students who were caries free were excluded without giving specific reasons, and the controls were not given placebo treatment at all due to administrative difficulties. One of the major limitations of these studies is that the quantitation and statistical analyses for the total flora and levels of *S. mutans* were based on non-standardized method for collecting plaque samples. Thus, the study conclusions were questionable.

While the vancomycin studies contribute to the overall knowledge base, use of this agent in the management of dental caries would be considered as contraindicated due to the real possibility of fostering bacterial resistance to vancomycin, especially within the enterococci where vancomycin-resistant strains are serious life-threatening pathogens.

## RECOMMENDATIONS AND COMMENTS

1. In agreement with the RTI/UNC assessment, none of the two dozen or so trials involving the chemotherapeutic management of dental caries is well designed or executed to warrant endorsement for clinical use at this time. Instead, these studies were “proof of concept” demonstrations based on what is perhaps an incorrect assumption, i.e., reductions in mutans streptococci leads to reductions in caries.
2. A recent study by Forgie and coworkers, which was published after 1999, constitutes perhaps the best example of a well-designed and executed clinical trial.<sup>3</sup> Here, a 10 percent chlorhexidine varnish was applied to the dentition of 13-15 year old caries active children. While these authors demonstrated a reduction in mutans streptococci, the treatment had no effect on caries increments. Several explanations can be offered for this lack of efficacy, such as duration and frequency of applications, but the lack of concordance between MS reduction and caries reinforces the findings of studies reviewed by the RTI/UNC.
3. Although the collective findings of studies reviewed suggest modest to no reductions in caries after antimicrobial therapy, important information may be gleaned from these studies in designing future studies. For example, surrogate endpoints such as the effect of antimicrobials agent on mutans streptococci levels correlate poorly with eventual caries reductions. Other surrogate markers that better correlate to caries reductions are needed for intermediate landmarks of efficacy.

4. The use of various fluoride preparations as antimicrobials has not achieved acceptance in the dental community. In addition, *in vitro* studies and animal model studies suggest fluoride may exhibit additive or synergistic effects on antimicrobial properties and caries reduction. These combinations include chlorhexidine -fluoride and iodine-fluoride combinations.
5. Several studies suggest that antimicrobial treatments may be less effective because of their inability to penetrate into the depths of subclinical lesions, margins of restorations, or pit and fissures. Obtunding these inaccessible sites with sealants or bonded restorative materials prior to disinfection may enhance the effectiveness of antimicrobial regimens
6. Reductions of cariogenic bacteria in mothers for the purpose of interfering or delaying transmission to the child has been shown to reduce both transmission and caries in children. These results, however, have not been confirmed by others. Nonetheless, the concept warrants consideration and refinement, as it constitutes a primary preventive approach prior to the onset of caries in children.
7. The limited and judicious use of antimicrobials based upon ecological aspects of acquisition/transmission may be a more targeted method of shifting the ecological balance from a caries-prone to a non-caries biofilm.
8. The rationale for use of chemotherapeutic agents for the control or prevention of dental caries will necessitate a more holistic understanding of the plaque microcommunity. Shotgun suppression of the entire flora, without acknowledging the overall effects on

ecology, is unlikely to succeed. Chemotherapeutic approaches must be better targeted against specific microbes with the goal of re-establishing an ecologically stable non-cariogenic plaque. In addition, chemotherapy will need to be coupled to mechanical measures to reduce or eliminate reservoirs for re-colonization.

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